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14. ABSTRACT
The proposed and executed effort of this project was a literature review of neurophysiological outcomes of mTBI. There are two sections in this report. The first section is an overview of neurophysiological outcomes of mTBI that have been addressed in the literature that are not related to cortical metrics. The second section addresses literature related to cortical metrics. Specifically, references of measures that can be routinely collected with the Brain Gauge (the device used to collect tactile based neurosensory assessments) were identified, collated, and excel spreadsheets were generated that describe the contents of these references.

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Neurophysiological outcomes of mTBI – Progress Report

The proposed and executed effort of this project was a literature review of neurophysiological outcomes of mTBI. There was no original research proposed or executed (i.e., no human subjects or animal research in this effort). There are two sections in this report. The first section (Part 1 - directly below) is an overview of neurophysiological outcomes of mTBI that have been addressed in the literature that are not related to cortical metrics. Subsequent sections address literature related to cortical metrics. Specifically, references of measures that can be routinely collected with the Brain Gauge (the device used to collect tactile based neurosensory assessments) were identified, collated and excel spreadsheets were generated that describe the contents of these references. These measures include temporal order judgement, reaction time, and timing perception and how those measures have been used for detecting deficits in information processing mechanisms in a number of cohorts, including mTBI.

Part 1.

A review of the literature on the topic of concussions shows what common sense should tell you—every concussion is different, so the physiology of concussions cannot be boiled down to a single, or even a single group, of statements. Physiological effects of concussion fall along a spectrum and are very much dependent on where on the head the person was hit, the force of the impact, the time since impact, total number of impacts the person has sustained, time between repeated impacts, age, and gender. Thus, data from the literature is varied and spans a wide range methods on study design and the subjects involved in testing.

Due to inconsistencies in subject injuries and time since impact, controlled animal studies can be of great help when evaluating physiological impacts of concussion. Animal studies, especially with rodents, allow for larger sample sizes, controlling the type and location of impact, investigating histological changes, and more standardized multiple impact studies. Homogenizing injuries and treatments allows for making more concrete statements about the impacts of concussion. For example, Huang et al. (2013) found greater tissue damage when impacts were administered 3d apart compared to 7d, and animals subjected to TBIs 3d apart still showed behavioral signs of concussion 1 month later while the other treatment group did not. On the other hand, concussions in humans are heterogeneous, with multiple sites of injury, torque, and confounding factors common due to the nature of injury. Thus looking at effects of a single impact at a single site does not necessarily reflect concussions that occur outside of a controlled environment. Furthermore, as reviewed by Shultz et al. (2016), there are many translational inconsistencies to consider when moving from animal models to humans, especially when using rodents. For example, because a rodent life span is vastly shorter than the average human, translating time between multiple impacts between species is not necessarily one-to-one.

Similarly, metabolism and pathophysiology differ greatly, making it important to interpret results with caution when relating to human TBI.

Balance is one measure commonly evaluated post-concussion, especially in athletics, although evidence and support as this being a reliable measure is limited. Studies have found that failure to pass the Balance Error Scoring System (BESS) test can be an effective measure for detecting concussions immediately following an impact (Guskiewicz et al. 2001, McCrea et al. 2005, Broglio & Puetz 2008), however false negatives are common—Guskiewicz et al. (2000) report only 30% of head injury patients show signs of balance problems immediately after injury. Furthermore, of those that do show alterations in balance, BESS scores usually return to equal or better than that of healthy controls within a week following the concussion, likely due to a practice effect and/or inter- and intra- rater variability (Riemann & Guskiewicz 2000, McCrea et al. 2003, Valovich et al. 2003, Vaolovich et al. 2004, Finnoff et al. 2009, Sheehan et al. 2011). Thus, reduced balance immediately after impact may be an effective way to quickly assess if a concussion has occurred, but not usually effective at determining when the injury has healed.

In contrast, imaging studies have shown altered brain function in the absence of diminished performance on cognitive tests in concussed individuals, but to date, no imaging study has been able to establish a significant link between continuing, chronic symptoms and physiological changes that result from concussion (reviewed in Shultz et al. 2016). While some concussions/TBI result in brain lesions, intracranial bleeding, or skull fractures detectable by CT or standard MRI, most are completely undetectable using these methods, especially when the injury is mild. Less than 10% of CT scans of concussion patients reveal any abnormality, and MRI abnormalities are present in only 10-57% of patients (reviewed in Bazarian et al. 2006). Keeping in mind that these studies included patients with severe TBI, the use of these standard imaging techniques appear to be very limited in their ability to diagnose concussion and mTBI.

Another MRI method capable of detecting physiological outcomes of concussion includes ASL, or arterial spin labeling, which can directly measure cerebral blood flow. This method has been used in relatively few studies to date to evaluate mTBI/concussion, with conflicting results found between studies. Wang et al. (2016) found decreased cerebral blood flow 24 hours after concussion in concussed athletes. After 8 day, when clinical symptoms had resolved, they documented that cerebral blood flow had decreased further from 24 h post-concussion levels, adding more evidence that the disappearance of clinical and neurocognitive symptoms commonly used to determine return to play is not necessarily an indicator that the athlete has fully recovered. However, Doshi et al. (2015) found that a week after concussion, athletes showed increased blood flow in the left striatum and frontal and occipital lobes compared to healthy controls. With small sample sizes (n=7 concussion group, n=12 control), this suggests that more studies are needed to determine the accuracy of this method.

Using fMRI pre- and post-concussion, Jantzen et al. (2004) found increased activation of the parietal and lateral frontal and cerebellar regions within 1 week of concussion, even in the absence of a change in cognitive performance postinjury. Similarly, McAllister et al. (1999) observed similar performance of concussed and control individuals, but there were differences in the activation patterns during working memory tasks between the two groups. Chen et al. (2004) also noted differences in working memory activation patterns despite normal performance in concussed individuals. Specifically, more activation was seen outside the area of interest that was not present in control groups, and BOLD (Blood Oxygen Level Dependent) responses were different between the two groups.

Changes in functional connectivity have been widely cited as a result of both acute and chronic concussion/mTBI. However, the details of such changes are not always clear, straightforward, or cohesive between studies depending on subjects used. Nevertheless, to make a generalization, it has been shown that even in asymptomatic patients, connectivity, as measured by resting state fMRI, is reduced post-concussion and is inversely related to the number of TBIs sustained by the individual (Johnson et al. 2012). In their review of the topic, Chong and Schwedt (2015) were only able to conclude that functional connectivity does appear to change following concussion, including alterations in the default-mode network (DMN), but they were not able to make any other broad generalizations on the topic.

Other techniques including EEG and DTI can also be effective at detecting altered brain function post-concussion. Again, results and conclusions are varied depending on severity of concussion and amount of time elapsed since impact. In general, DTI has documented changes in diffusivity both acutely and chronically (6 months post impact) (Henry et al. 2011), and Lipton et al. (2009) showed a correlation between executive function and activity in the dorsolateral prefrontal cortex with acute concussion cases (< 2 weeks post impact).

Another imaging method, PET, or more specifically [^{18}F]fluorodeoxyglucose (FDG)-PET, is able to detect changes in cortical metabolism post-concussion. As is the case with most concussion research, studies vary widely in severity and location of injury, and sample sizes are rarely big enough to make strong general conclusions. In their review of this topic, Byrnes et al. (2014) concluded that post-concussion, patients show a decrease in brain metabolism, either globally or regionally that can last days to months, with some indication of correlation with degree of injury.

Alterations in brain metabolite concentrations can be measured using magnetic resonance spectroscopy (MRS) as an indicator of disrupted metabolism within the brain (reviewed in Honce et al. 2016). This method has been used to show changes in creatine and glutamate/glutamine complex levels in asymptomatic high school football players following impact (Poole et al. 2014). Furthermore, the use of NAA/Cr and NAA/Cho ratios have been

successful in showing that athletes are not always fully recovered once clinical symptoms have resolved, and in athletes who sustain a second hit before metabolite ratios return to normal, recovery time from the second impact is significantly longer than in those who sustain a second hit after fully recovering from the first injury, as determined by MRS. Also, metabolite imbalances that were not present acutely can present up to 6 months post-injury (reviewed in Honce et al. 2016).

More recently, the use of blood biomarkers as an indicator of concussion has been more thoroughly investigated as a way to detect concussion more easily, cheaply, effectively, and without the radiation exposure of CT scans (reviewed in Zetterberg et al. 2013, Mondello et al. 2014, Plog & Nedergaard 2015, Huang et al. 2016, Kawata et al. 2016, Kulbe & Geddes 2016, Zetterberg & Blennow 2016). While they show more promise to accurately diagnosing mild TBI than imaging, they still have their downsides and there are currently no biomarkers tests available that can definitively detect mild concussions. In order to be effective, biomarkers must be present in detectable quantities in some body fluid, and they should be specific to CNS injury. As noted previously, each TBI patient is different and effects of impact are different in each patient depending on a number of factors. It is therefore difficult to find a single biomarker that can be used as a "gold standard" for TBI detection, particularly when considering that these molecules must 1) pass through the blood brain barrier (BBB) in detectable levels to be reliably and accurately measured in blood samples 2) measurement errors are possible at many levels including collection, storage, and measurement of samples 3) most of the biomarkers being investigated currently are not exclusive to head trauma and elevated levels can be an indicator of orthopedic or other peripheral injury. Analyzing CSF samples as opposed to blood can bypass some of these problems, but it is much more invasive and risky, and sampling cannot be repeated as often as a blood sample. That being said, there are some biomarkers that have been investigated and show some potential for helping to clarify the picture of what is going on inside a patients head following impact. Specifically, S100-β, neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP), are the most thoroughly studied biomarkers that show potential, and all have been extensively reviewed (Zetterberg et al. 2013, Mondello et al. 2014, Huang et al. 2016, Kawata et al. 2016, Kulbe & Geddes 2016, Pan et al. 2016, Zetterberg & Blennow 2016). While they show the more promise than other suggested biomarkers, they still have their downsides and have shown mixed results in their efficiency as an indicator of mTBI.

S100-β is a marker of activated astrocytes and is moved into the bloodstream by bulk flow via the glymphatic system (Plog et al 2015). However, it is also found in peripheral sources, including chondrocytes, adipocytes, and exocrine cells and elevated blood levels have been detected in patients following ischemic reperfusion injury, bone fractures, as well as in people with mood disorders (reviewed in Pan et al. 2016).

NSE is an enzyme involved in glycolysis, mostly within neurons, and it is upregulated in response to axon damage in order to maintain homeostasis. While multiple studies have shown significant increases blood levels of this protein following moderate and severe TBI, it has not been shown to be useful in detecting mild TBI. Furthermore, increased serum NSE has been detected following hypoperfusion, liver damage, kidney damage, migraines, and bone fractures, further limiting its ability to accurately detect TBI (Reviewed in Kawata et al. 2016).

GFAP is a structural protein found in astrocytes. With neurotrauma, astrocytes show morphological changes, including increases in size, which involves increased GFAP production, plus GFAP can be shed following astroglial damage either due to mechanical forces or necrosis (reviewed in Kawata et al. 2016). Unlike most other suggested biomarkers, this protein is not found outside the nervous system, making its presence in blood more specific to neurotrauma. Furthermore, multiple studies have shown that it can be found in detectable levels in mTBI patients, and levels appear to be correlated with severity of injury. This protein appears to hold more promise in detecting TBI, but it has not been studied as extensively as S100-β and many studies that have been done have had relatively small sample sizes. Additional studies are needed to verify its specificity and sensitivity, as well as establish how long it remains present in the blood (reviewed in Kawata et al. 2016, Kulbe & Geddes 2016, Pan et al. 2016).

With more testing and validation, using fluid biomarkers could be a valid part of determining when head trauma has occurred and/or when a patient has recovered. However, there are many confounding factors to consider and many shortcomings to this method, it has even been suggested that this method may never work to the degree that others have suggested due to the glymphatic system (Huang et al. 2016). In fact, Plog et al. (2015) found that serum levels of S100B, NSE, and GFAP were not elevated following experimentally induced TBI in mice when the glymphatic system was blocked. The potential for a false negative test result from any biomarkers measured from blood is a thus concern, particularly given that sleep deprivation (a possible side effect of TBI) as well as TBI in and of itself decreases glymphatic system activity (Iliff et al. 2014, Plog et al. 2015). Furthermore, even if proteins make it into the bloodstream, they will eventually degrade, be cleared by the hepatic and renal systems, and they can bind to carrier proteins, making standard measurement methods inaccurate (reviewed in Plog & Nedergaard 2015).

Huang et al. (2016) suggests a way around the obstacle of the glymphatic system by noting that TBI of any origin causes breakdown of the blood brain barrier (BBB). In theory, increased levels of circulating brain microvascular endothelial cells (cBMEC), the main constituent of the BBB, could be an indicator of TBI. But again, this suggestion has its drawbacks as increased cBMEC levels could be confounded by a number of other factors that also cause BBB breakdown, including (but not limited to) nicotine and HIV.

Recent advances in TBI detection have been in the field of molecular biology, using micro RNA (miRNA) as a biomarker for TBI. While studies in this area are limited, this method does appear to hold more promise than protein biomarkers discussed previously. Using miRNA as opposed to proteins allows for detection of the biomarker at lower concentrations, miRNA is less susceptible to degradation, both before and after sampling, evidence shows that there are more biomarkers that are specific to TBI and not influenced by peripheral damage, and there are miRNA markers that have been shown to be able to differentiate between mild, moderate, and severe TBI in mouse models and in humans (Balakathiresan et al. 2014, Sharma et al. 2014, Bhomia et al. 2016, Harrison et al. 2016, Sun et al. 2016, Taheri et al. 2016,).

Specifically, Sun et al. (2016), found that expression of the miRNA miR-23b was downregulated in plasma of TBI patients relative to healthy individuals. Bhomia et al. (2016), using blood samples from human subjects with either mTBI, severe TBI, orthopedic injury, or healthy controls, found 8 miRNAs specific to mTBI, 10 specific to sTBI, and 10 specific to orthopedic injury. In TBI patients, expression levels of most miRNAs showed a direct correlation to severity of injury as indicated by CT lesions. These results seem promising, but sample sizes were small (n=8/group) and all sampling was done 12-48 h after injury, meaning the ability to assess TBI status over time to track progress and recovery remains unknown. Further studies must also be done to determine if these miRNAs could also be present in other neurological conditions that may co-occur with TBI. For example, PTSD has been shown to have its own miRNA signature (Balakathiresan et al. 2016).

In summary, it has been widely documented that concussions/TBI cause a wide range of alterations in brain function. However, this injury is extremely heterogeneous in nature, making it difficult to make broad generalizations. Individual injuries can affect different parts of the brain in different ways depending on factors such as the location and intensity of impact, the number of previous concussions sustained, and time between impacts, so any method used to assess the injury must be able to do so irrespective of each of these factors. One generalization that can be made, however, is that changes in neurophysiology following concussion rarely are completely resolved at the same time that clinical symptoms disappear, and sustaining a second head injury before the first has resolved can drastically increase the severity of the injury. Thus, it is important to establish a method to accurately detect and track progress in order to prevent re-injury in an already injured brain.

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Part 2.

Temporal order judgement (TOJ) defines an individual's ability to determine the order of two stimuli delivered to the peripheral sensory sheet. This ability is largely attributed to frontal-striatal pathways and TOJ is impacted in mTBI when that part of the cortex is impacted. Some neurological groups do particularly poorly in this task (e.g., schizophrenia and dyslexia). The contents of the TOJ references below are summarized in an excel spreadsheet.

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